The use of formalin-fixed, paraffin-embedded lymph node samples for the detection of minimal residual disease in mantle cell lymphoma.

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Letter to the editors

There is a growing evidence regarding the usefulness of minimal residual disease (MRD) monitoring in mantle cell lymphoma (MCL) (Pott, 2011). MRD assessment in MCL can be performed either at the gene expression level using $CCND1$-$IGH$ transcript (Pott, 2011), via $CCND1$ overexpression (Brizova et al, 2008) or at the DNA level. Quantitative polymerase chain reaction (qPCR) for clone-specific immunoglobulin ($IGH$) gene rearrangement is currently the most sensitive and robust tool for MRD detection and has been thoroughly standardized for use in acute lymphoblastic leukaemia (ALL) (van der Velden et al, 2007). Circulating lymphoma cells are present in most MCL cases at diagnosis, at a median 6% in the peripheral blood (PB) and 7% in bone marrow (BM) (Pott et al, 2010). Therefore, a clone-specific target ($IGH$ or $CCND1$-$IGH$) can be derived from diagnostic BM or PB. This material can be further used as a dilution standard for MRD quantification at later time points. Using this approach, MRD assessment is possible in 80-85% of MCL cases (Pott, 2011). In the remaining cases, there is either no BM/PB infiltration or it is too low for the reliable identification of a clonal $IGH$ target on the background of normal B lymphocytes. In those cases, a fresh diagnostic lymph node sample could serve for target identification and dilution series construction, but this is rarely
available, especially in a multi-centre setting. Unlike fresh samples, formalin-fixed, paraffin-embedded (FFPE) tissues are used routinely for histopathological diagnosis and are usually archived in diagnostic centres. However, concerns regarding the use DNA from FFPE samples include the poor integrity and quantity of isolated DNA and the impossibility of quantifying the initial lymphoma infiltration for setting the dilution curve.

Here, we describe a method for MRD quantification based on FFPE tissue samples than can reliably detect MRD in MCL patients (detailed in the Supporting Information). The DNA was isolated from FFPE sections and checked for integrity via amplification of differently sized fragments (van Dongen et al, 2003) and for amplificability via the ALB control gene (Pongers-Willemse et al, 1998). The lymphoma infiltration in the lymphoma section was estimated using CCND1 staining. Further steps of the method are identical with the setting of patient-specific MRD assay from BM/PB and include screening for clonal IGH or CCND1-IGH rearrangements, sequencing of junctional regions, design of patient-specific primers and optimization of qPCR assays (Verhagen et al, 2000; van Dongen et al, 2003; Pott et al, 2013).

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Taken together, this study demonstrated that it is possible to establish reliable MRD assays even with small, archived FFPE biopsy samples. This can be clinically relevant in approximately 20% of MCL patients without a MRD target because it can clearly determine the presence or absence of lymphoma dissemination both at diagnosis and during the clinical course of the disease.


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